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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,564	11/07/2000	Florian Kern	KREISLER1089	5234

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/600,564	KERN ET AL.	
	Examiner	Art Unit	
	ROBERT A. ZEMAN	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-27* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 11-12-2008 are acknowledged. Claim 14 has been amended. Claims 14-27 are pending. Claims 22-26 remain withdrawn from consideration as being drawn to non-elected invention(s). Claims 14-21 and 27 are currently under examination.

Claim Objections Maintained

The objection to claim 27 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 14 is maintained for reasons of record.

Applicant argues:

1. The objection is premature as neither of the claims has been allowed.

Applicant's arguments have been fully considered and deemed non-persuasive.

As outlined previously, when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections Withdrawn

The rejection of claim 14 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "selection and proliferation" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14-21 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237) for essentially the reasons set forth in the previous office action in the rejection of claims 14-19, 21 and 27.

Applicant argues:

1. Specific elimination occurs following specific activation and is based on the deprivation of nutrients and growth factors to the “non-activated” cells by the “activated" cells.

2. Basing a rejection the based on claim language drawn to "particular" T cells is a semantic game and not reason for rejecting a claim.

3. That since the time period specified by applicant in his method is 4 times shorter than the shortest time period specified by Yanagisawa et al. and because of the obvious advantage of performing the entire procedure within one working day; applicant has demonstrated a significant and useful difference between his invention and the process of Yanagisawa et al.

4. No activation marker is measured by Yanagisawa et al.

5. Yanagisawa et al. only allows mapping of the epitopes at a rough population level not at the single cell level.

Applicant’s arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, while Applicant is correct in his assertion that the activation of a given T cells will lead its increased consumption of nutrients due to proliferation, his assertion that this increased consumption leads to the specific starvation of non-activated clones is erroneous. Contrary to Applicant's assertion, the effects of nutrient deprivation would be applied equally to all cells within a given "culture". Over time any the percentage of proliferating cells within said culture would increase due to their expanding numbers. However, the sheer number of cells eliminated due to "starvation" would be greater in the stimulated population as overall numbers would be greater. Consequently, there is no specific elimination of "non-stimulated" T-cells. Finally, it should be noted that both stimulated and non-stimulated cells would be subject to the effects of nutrient deprivation at the same time.

With regard to Point 2, Applicant's arguments are not germane as the instant claims do not contain claim language drawn to "particular" T cells.

With regard to Point 3 Applicant is reminded that the instant claims recited no definite time periods. The independent claims define the incubation time as a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the specific elimination of stimulated T cells do not occur". This time period would necessarily vary from cell population to cell population. More importantly, the upper end of the claimed "range" is defined by the "the specific elimination of stimulated T cells" not occurring. It is deemed that since the cellular functions and surface markers of the stimulated cells are effectively measured by Yanagisawa et al., said cells have not

be "eliminated". Moreover, contrary to Applicant's assertion, the instant claims do not require the claimed method to be performed "within one working day".

With regard to Point 4, Yanagisawa et al. disclose the measurement of multiple T cell markers including CD4 (see pages 228-229).

With regard to Point 5, flow cytometry measures each cell individually. Moreover, Applicant is reminded that the requirement for the measurement of activation markers to be on the individual cell level is only present in claim 15.

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the elimination of stimulated T cells do not occur".

As outlined previously, Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chair repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR $V_{\beta)}$ was measure before and after culturing (see page 229).

With regard to the limitation that the incubation time be sufficiently short so that selection, proliferation and the specific elimination of stimulated T cells does not occur, it is deemed, in absence to evidence to the contrary, that since the active expression of cell surface markers and are measured on the stimulated T cells, said cells could not have been eliminated.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 14-21 and 27 under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237) and Picker et al. (Blood, 1995, Vol. 86 No. 4, pages 1408-1419 -- IDS) is maintained for reasons of record.

Applicant argues:

1. The only conclusion that can be drawn from Picker et al. is that the activation of T-cells by super antigens can by measured at a single cell level if the staining is performed intracellularly following retention of cytokines in the cell.

2. Even if the skilled artisan followed the Examiner's suggestion, he would not have duplicated the instant invention as the method of Yanagisawa et al. fundamentally differs from the instant invention with regard to the duration of incubation.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, Picker et al. disclose a multi-parameter flow cytometric assay that allows the simultaneous determination of an individual T cell's ability to produce multiple cytokines and its phenotypes after a short (4 to 8) *in vitro* incubation with an activating stimulus (antigen) [see abstract]. Picker et al. further disclose that said T cells could be contained in peripheral blood samples (see page 1409).

With regard to Point 2 Applicant is reminded that the instant claims recited no definite time periods. The independent claims define the incubation time as a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major

histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the specific elimination of stimulated T cells do not occur". This time period would necessarily vary from cell population to cell population. More importantly, the upper end of the claimed "range" is defined by the "the specific elimination of stimulated T cells" not occurring. It is deemed that since the cellular functions and surface markers of the stimulated cells are effectively measured by Yanagisawa et al., said cells have not be "eliminated". Moreover, contrary to Applicant's assertion, the instant claims do not require the claimed method to be performed "within one working day".

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC)

molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the elimination of stimulated T cells do not occur".

As outlined previously, Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chair repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR $V_{\beta)}$ was measure before and after culturing. Additionally the production of IFN-γ, IL-10, IL-5 and IL-4 was measured (see page 229).

Yanagisawa et al. differs from the instant invention in that the cytokine levels are measured by ELISA.

Picker et al. disclose a multiparameter flow cytometric assay that allows the simultaneous determination of an individual T cell's ability to produce multiple cytokines and its phenotypes after a short (4 to 8) *in vitro* incubation with an activating stimulus (antigen) [see abstract]. Picker et al. further disclose that said T cells could be contained in peripheral blood samples (see page 1409).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the flow cytometry method of Picker et al. in the epitope mapping method of Yanagisawa et al. in order to take advantage rapid ability to determine the functional potential (i.e. response) of phenotypically distinct T cell subsets.

One would have had a reasonable expectation of success since Picker et al. disclose that the "simplicity and rapidity" of their detection technique coupled with the widespread availability of flow cytometers and T cell phenotyping antibodies suggest that their technique could be broadly applicable to the evaluation of immune status (see page 1418). Moreover, given that the use of flow cytometry to measure cytokine levels is well known in the art (as acknowledged by Applicant) yielding predictable results, it is obvious for the skilled artisan to use flow cytometry in the methods of Yanagisawa et al. (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert A. Zeman/
Primary Examiner, Art Unit 1645
February 16, 2009